## REMARKS

Claims 20, 49, 51, 56, 57, 59 and 65-67 are pending in the subject application. Applicants have herein amended claims 20 and 65 to specify that the mesenchymal stem cells incorporated with a nucleic acid which encodes a HCN2 channel "form[ ] a gap junction with a cell of" a heart. The amendments are fully supported in the specification by Figures 3, 4, and 10 and their descriptions at page 6, lines 15-26 and page 7, line 28-page 8, line 18. Claim 66 is amended to correct a grammatical error. Claims 66 and 67 are amended to refer to claim 65. Thus, Applicants maintain that these amendments do not present new matter. Accordingly, Applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 20, 49, 51, 56, 57, 59 and 65-67, as amended, will be pending and under examination.

Applicants thank the Examiner for the courtesy extended during the interview held on April 15, 2008. The remarks which follow reflect, in part, the discussions held during this interview.

### I. Examiner Interview

In an interview held on April 15, 2008 between Examiner Anoop Singh and Applicants' Representatives Carmella Stephens and Lawrence Frank, the pending claim rejections were discussed. The Examiner clarified that the outstanding rejections under 35 U.S.C. § 112 relate to the wording of claims 20 and 65 and to the relevance or "nexus" of a demonstrated ability to influence a dog heart's rhythm to the treatment of heart arrhythmias in humans.

The references on which the obviousness rejections are based were also discussed. The Applicants contended that, at the time of the invention, no motivation existed to combine the references or to modify the prior art to arrive at the claimed inventions. Applicants further contended that the person of ordinary skill in the art would not have had a reasonable expectation of success at the time of the invention in modifying the prior art to arrive at the claimed inventions, particularly in light of unpredictability of the art, which the Examiner has pointed out. The Examiner appeared to acknowledge the merit of this position. In response, the Examiner cited Qu et al. (89 Circ. Res. e8-e14 (2001) (submitted in the accompanying IDS) for

motivation to combine with a reasonable expectation of success.

No resolution was reached.

## II. Rejection of claims 20 and 65 under 35 U.S.C. § 112, Second Paragraph (Indefiniteness)

Claims 20 and 65 were rejected for indefiniteness for reciting "is capable of forming." The claims have been amended to recite instead "forms." This rejection should therefore be withdrawn.

## III. Rejection of claims 49, 51, 56-57, 59 and 65-67 under 35 U.S.C. § 112, First Paragraph (Enablement)

The Examiner concedes that the specification provides guidance with respect to directly injecting hMSC transfected with nucleic acid encoding HCN2 polypeptide into the anterior left ventricular wall of canine heart, resulting in expression of HCN2 and generation of pacemaker rhythm in the canine heart. *See* Office Action at 4. The Examiner further concedes that the specification and the Plotnikov reference that the Applicants cited in the previous amendment (August 13, 2007) provide "adequate guidance for a method of inducing pacemaker current in mammalian heart." *See id.* at 6.

Nevertheless, Claims 49, 51, 56-57, 59, and 65-67 have been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The enablement rejection appears to rest on three bases.

First, the office action states that treating a cardiac rhythm disorder or increasing the pacemaker current in a mammalian heart, especially in humans, is complex and unpredictable. The rejection recites the attributes of an ideal biological pacemaker, suggesting that the claims are not enabled if these attributes are not achieved. These attributes include continuous function throughout the treated individual's life, being "fail-proof," providing a physiological heart rate, "which may change based on the metabolic needs of the individual," and the absence of "any inflammation." *See* Office Action at 4. Further, the sinus nodes should be "returned to normal function," and there should be little or no loss of the implanted cells, no differentiation of the

implanted cells, and long-term control of the level of transgene expression within the implanted cells. *See id.* at 4-6. Further, according to the Office Action, even though the claims recite the use of mesenchymal stem cells, the "problem of potential differentiation to cell of other lin[e]age still exists as discussed before (supra), which would be critical for maintaining any stable physiologic rhythm."

Second, the Office Action also finds no "nexus" between the disclosed injection of the MSC composition and delivery by "any" means such as topical or via catheter. *See* Office Action at 4. Further, the Office Action finds no correlation of delivery to anterior left ventricular wall with delivery to any other part of the heart, such as the atrium or Purkinje system. *See id.* at 4-5.

Third, the Office Action asserts that there is no evidence to support extrapolation of the canine model that the specification discloses to "any mammalian heart for therapeutic purpose without undue experimentation." *Id.* at 6. The Office Action asserts that, since "vagal stimulation in dogs does not represent a cardiac rhythm disorder in a mammal, the specification fails to provide sufficient guidance, with regard to the breadth of the claims." *Id.* at 7.

For the reasons set forth below, Applicants contend that the claims are enabled by the specification. Applicants note at the outset that the relative skill of those in the art to which the instant application is directed is believed to be that of a person having a Ph.D. or similar experience in molecular biology as it relates to cardiology or a related field, or having an M.D. or similar experience with a specialty in cardiology or a related field, having in addition an understanding of the electrical conduction system of the heart and/or the functioning of ion channels and related proteins.

**A. The Specification's Disclosure**

As to the sufficiency of the specification's disclosure, Applicants provided in their previous reply of August 13, 2007 a summary of relevant portions of the specification and how it addresses the Examiner's rejections. This summary is set forth again below.

Applicants maintain that at the time the subject application was filed the HCN2

channel was well known and the specification teaches, by incorporation of relevant cited references, the sequences of HCN2 (see paragraphs [0037]-[0048] of the specification). Further, the specification teaches a person skilled in the art methods for isolation of homogeneous populations of MSCs, nucleic acids encoding the HCN2 channel that may be expressed in MSCs to induce or regulate a pacemaker current therein, and the use MSCs expressing a pacemaker ion channel to induce a pacemaker current in a heart. The specification provides a working example of the delivery into a canine heart of hMSCs transfected with a nucleic acid encoding a HCN2 polypeptide, resulting in the expression of functional HCN2 channels and the generation of a stable, idioventricular pacemaker rhythm in the canine heart. (*See* para. 0029 and Fig. 10). The use of a canine model is based on its cardiac size, tractability as a chronic model and similar electrophysiologic properties to those of human.

Further, Applicants directed the Examiner's attention to the published abstract of an article subsequently published as Plotnikov et al., Circulation 116: 706 (2007) (henceforth "Plotnikov"), which describes the injection of mHCN2-transfected hMSCs directly into left ventricular (LV) subepicardium of non-immunosuppressed adult dogs. Plotnikov reports that nests of hMSCs were found adjacent to the injection site but not at a distance. As noted by Applicants in their September 25, 2006 Amendment regarding the published abstract of this article, Plotnikov is a post-filing date reference that describes the results of experiments conducted in accordance with methods disclosed in the specification.

To the extent that Plotnikov includes experimental details not described in the specification, Applicants maintain that these details could be determined by a person of ordinary skill in the art without undue experimentation. Applicants maintain that one of skill in the art could readily determine the appropriate concentration of MSC cells which would be effective in the treatment of a particular cardiac disorder or condition. Such concentrations will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. The precise dose of MSCs to be employed in the method of treatment will also depend on the route of administration, and the seriousness of the disease or disorder, and can be decided according to the judgment of the practitioner and each patient's circumstances. Thus, Plotnikov may be properly cited to demonstrate that the disclosures in the specification as filed are

sufficient to enable a person skilled in the art to practice the invention being claimed without undue experimentation, *i.e.*, to demonstrate that the disclosure was enabling as of the filing date.

**B. Therapeutic Effect and Safety**

The rejected claims recite a method of expressing an HCN2 ion channel, a method of treating a cardiac rhythm disorder, a method of inducing a pacemaker current, and a composition (inappropriately rejected on the recited grounds, which relate to methods). The factors that the Office Action recites as demonstrating unpredictability relate to an ideal, permanent cure of the claim-recited conditions ("fail-proof," "without any inflammation"), not to expressing, treating, inducing, or a composition. It is unreasonable and not required under 35 U.S.C. § 112 that a method of treating or inducing a pacemaker current be held to the same standard as a method of curing.

"Treatment" is defined in the art as "medical or surgical management of a patient." Stedman's Medical Dictionary 1626 (25th ed. 1990). This definition clearly differs significantly from "cure." Applicants' claimed method is consistent with the dictionary definition. The use of the term "treatment" in the application is also consistent with this definition. For example, the specification states that a cardiac condition of a subject is considered "treated" when a heart cell of the subject is contacted with a composition comprising stem cells having certain attributes in an "amount sufficient to increase the current expression of the cell." *See* Application as published at ¶ 0012. Further, if "treatment" were properly understood as "cure," then the patent office would not have issued claims to "a method of treating lung cancer" (United States Patent No. 7,259,262), for which there is no known 100%-effective cure, or "a method for treating leukemia" (United States Patent No. 7,259,187), or many of the other over 47,000 issued patents that claim methods of treating. Applicants further note that even the traditional, mechanical pacemaker (as opposed to the instantly claimed biological pacemaker) or its prototypes would not meet the Office Action's standards ("fail-proof"), although patents on those devices and on their use to treat cardiac arrhythmias no doubt issued.

Thus, Applicants assert that treating a cardiac rhythm disorder or inducing a pacemaker current is not unpredictable, in view of the specification. The claims therefore should be

considered enabled. The specification provides sufficient guidance and examples to enable the person of ordinary skill in the art to make and use the claimed invention without undue experimentation, namely, to treat a cardiac rhythm disorder or to induce a pacemaker current as these terms are properly understood in view of the specification.

Regarding the Examiner's concern about the sustainability of a therapeutically effective level of HCN2 expression, Plotnikov teaches that physiological function of hMSC-based biological pacemakers occurred in 3-10 days and persisted throughout the 42 days during which the transplanted cells were monitored. In addition, no differentiation of hMSCs was observed in Plotnikov over the 42-day period[1], and there was no humoral or cellular rejection of hMSCs. The latter result is consistent with evidence that hMSCs are immunoprivileged (see Liechty et al. (2000) Nat. Med. 6: 1282-1286, attached as Exhibit 2 in the September 25, 2006 Amendment, at page 1283) and may actually suppress an immune response (see Javazon et al. (2004) Exp. Hematol. 32: 414-425, cited by the Examiner on a PTO-82 form, at page 417, right col.). Accordingly, Applicants maintain that the concerns raised by the Examiner do not undermine the enablement of the claimed invention.

The above reasoning applies at least as strongly to the claims that recite a method of expressing an HCN2 channel and a method of inducing a pacemaker current as to the claims that recite a method of treating.

The Office Action again points to the possibility of inflammation as a factor to consider in determining whether the claims are enabled.

Applicants assert that questions regarding the risk of side effects (*e.g.*, inflammation) are safety issues to be addressed and resolved in clinical trials. Regarding the degree of safety required under the patent laws, the MPEP states, with respect to satisfying the "how to use" element of the enablement requirement, that "[t]he Applicant need not demonstrate that the

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[1] Clearly, myogenic MSCs have the potential to differentiate into cardiomyocytes following transplantation into the heart. This is evident, for example, in two references cited in the Office Action: U.S. Patent Publication No. 20040087528 ("Levy") and Wang et al. (2000) J. Thorac. Cardiovasc. Surg. 120: 999-1005 ("Wang"). Whether or not MSCs transplanted into the myocardium differentiate is likely affected by factors including, foe example, the method of isolating the MSCs, the media on which the isolated cells are cultured, and the number of passages in culture before transplantation. Moreover, Applicants note that even if, *arguendo*, the transplanted MSCs were to differentiate into cardiomyocytes over a longer period, this would not be deleterious to the claimed methods.

invention is completely safe." MPEP § 2164.01(c). This passage also refers the reader to MPEP § 2107.03 (§ 2107 deals with the utility requirement), which states at part V.: "The Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs." The MPEP continues: "Thus, while an Applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness." MPEP § 2107.03 V. (emphasis added) (citing, among others, *In re Hartop*, 311 F.2d 249 (C.C.P.A. 1962), *In re Anthony*, 414 F.2d 1383 (C.C.P.A. 1969), and *In re Watson*, 517 F.2d 465 (C.C.P.A. 1975)).

The fact that inflammation might occur when the claimed methods are practiced, or that the claimed methods might not provide a fail-proof, physiological rhythm for the entire life of the treated patient, does not mean that the claimed methods are so unpredictable as to be not enabled, because, as noted above the claimed methods do not purport to provide a permanent cure of the treated condition. Further, treating as claimed is useful under 35 U.S.C. § 101 because it at least mitigates the detrimental effects of the treated condition, even if it does not provide a permanent, lifelong cure with no possibility of side effects or failure.

Thus, Applicants maintain that such safety concerns fall within the ambit of the Food and Drug Administration (FDA) rather than the Patent Office. Certainly, safety data obtainable from clinical trials are not required to satisfy the enablement requirement of a claimed invention. Thus, Applicants maintain that the Examiner's rejections of the claims as lacking enablement based, in part, on perceived safety risks issues is misplaced.

The Office Action points to various factors relating to effectiveness of the claimed methods to argue that the claimed methods are unpredictable and therefore not enabled.

Applicants point out that, according to the MPEP, "it is improper for Office personnel to request evidence...regarding the degree of effectiveness." MPEP § 2107.03 V. (emphasis added) (citing, among others, *In re Hartop*, 311 F.2d 249 (C.C.P.A. 1962), *In re Anthony*, 414 F.2d 1383 (C.C.P.A. 1969), and *In re Watson*, 517 F.2d 465 (C.C.P.A. 1975)). The Office Action's list of

reasons relating to alleged unpredictability on the ground that effectiveness is unpredictable (including but not limited to the provision of stable physiologic rhythm, the return of sinus nodes to normal function, and the long-term control of transgene expression level, *see* Office Action at 4-6) is in essence a requirement that the specification or Applicants disclose evidence of a high degree of effectiveness, and thus is contrary to the MPEP.

### C. Cell Delivery

As noted above, the Office Action asserts that delivery of cells to a heart by various routes including topical administration, administration via catheter, and administration by microinjection would not have been enabled by the disclosed method of injection of cells.

The Applicants disagree. The successful delivery by injection of hMSCs incorporated with HCN2 is exemplified in a working example in the specification. *See* Application at ¶ 0030. Other routes of delivery or administration were known in the prior art at the time of filing and disclosed in the specification, including topical application to the heart, microinjection, and catheterization. *See* Application at ¶ 0086 and Declaration of Michael R. Rosen ("Declaration") (submitted herewith) at ¶ 8. Further, the working example provides a means of determining the level of pacemaker activity obtained after using a means of administration other than that exemplified in the specification. *See id.* at ¶ 0030. Applicants conclude that, although the Examiner contends that the art is unpredictable, the provision of a working example combined with the state of the art and the relative skill of those in the art would have enabled the person of ordinary skill in the art to perform the recited methods using various means of delivery without undue experimentation.

As noted above, the Office Action contends that delivery to any part of the heart other than the left ventricular wall is, such as the atrium or Purkinje system, is not enabled by the application. Applicants disagree.

The application provides a working example of delivery of hMSCs incorporated with HCN2 to the anterior left ventricular wall of a dog's heart, resulting in induction of pacemaker current under the experimental conditions. *See* Application at ¶ 0030. The specification further discloses that contacting a cell of the heart generally with such stem cells can treat a cardiac

condition in a subject, such as conduction block, complete or incomplete atrioventricular block, and sinus node dysfunction, and can induce a current in the heart or a cell of a subject. *See id.* at ¶¶ 0081, 0083-0084, 0087, 0089. In view of the specification and given the relative skill of those in the art, the person of ordinary skill in the art would have been able to contact a cell of the heart with hMSCs incorporated with HCN2 and thereby treat such a condition or induce such a current. *See* Declaration at ¶ 0010. Moreover, in view of the disclosed example, the person of ordinary skill in the art would have been able to determine without undue experimentation the level of pacemaker function obtained following such contacting. Applicants conclude that, in light of the relative skill in the art, the state of the prior art, and the application disclosure, although the Office Action contends that the art is unpredictable, the person of ordinary skill in the art would have been able to practice the full breadth of the claims without undue experimentation.

### D. The Canine Heart as a Model for the Human Heart

Applicants contend that the induction of a pacemaker current in a dog's heart, as described and exemplified in the specification, would have enabled the treatment of a cardiac condition in a human, or the induction of a pacemaker current in a human, under 35 U.S.C. § 112, first paragraph, because, at the time of filing, the person of ordinary skill in the art recognized the dog heart as a model for the human heart. *See* Declaration at ¶ 11. It was known at the time of filing that the dog and human heart are similar to each other in a number of ways relevant to the claimed invention, including having a similar range of heart rates (from about 40 to about 180 beats per minute) and exhibiting similar autonomic responsiveness. *See id.* The specification's disclosure and guidance, including the example of inducing a pacemaker current in a dog heart, in view of the relative skill in the art and the state of the prior art, therefore would have enabled the person of ordinary skill in the art to perform the claimed methods without undue experimentation.

Applicants therefore respectfully request that the rejection of claims 49, 51, 56-57, 59, and 65-67 for lack of enablement be withdrawn.

## IV. Rejection of claims 20, 49, 57, and 65-67 under 35 U.S.C. § 103 (Obviousness)

Claims 20, 49, 57, and 65-67 remain rejected as allegedly obvious over the Levy et al., Marban et al., Jansen et al., and Wang et al. references raised in the previous office action.

**A. Levy**

The pending Office Action argues that Levy teaches "a method that uses hMSCs that could be transformed so as to contain a gene of interest," citing paragraph 58 of the reference. *See* Office Action at 13. The Office Action also points to Levy paragraphs 0027 (stating that the invention expands on known reverse gene therapy methods), 0031 (the method uses MSCs, including MSCs that express wild-type hMirp1 and the Q9E-hMirp1 mutant), and 0109 (MSCs can be transformed outside the body by the reverse gene therapy compositions and methods and then returned to the body from which they originated or administered to another body). In sum, the reference is cited for its teaching that reverse gene therapy methods can be used with MSCs.

Applicants contend that Levy is unrelated to the present invention because it discloses a method of reverse gene therapy that entails the use of a dominant negative or otherwise improperly functioning form of a protein to inhibit the proper functioning of other proteins or cellular components. *See* Levy ¶ 0010-0011, 0081. In contrast, the present invention entails the use of a protein to provide increased activity of that same protein, not to reduce the activity of other proteins. In fact, Levy provides the purportedly novel reverse gene therapy method as a solution to the "shortcomings of current gene therapy strategies" which "have typically involved delivery of," for example, a nucleic acid that encodes a "normal (i.e. wild type) component of a cell." Levy ¶ 0009. Levy thus in fact teaches away from the claimed methods (and consequently also teaches away from the compositions used therein), which entail delivering HCN2-encoding nucleic acids incorporated into MSCs.

**B. Marban**

The Office Action cites Marban for disclosing a composition of modified cells and a method that entails administering genetically modified cells to heart tissue. The Office Action alleges that the genes can be HCN channels, citing paragraph 0064. See Office Action at 9.

Applicants point out that the specific disclosure in Marban regarding use of HCNs relates

to the use of a dominant negative mutant form of HCN1 to suppress normal channel activity. This mutant HCN1 "inhibited HCN2 in a dominant-negative manner." See Marban ¶ 0062. Further, Marban discloses a laundry list of polynucleotides that can be used in the invention, among which are included HCN1 and various connexins, sodium channels, potassium channels, and calcium channels, and/or subunits thereof, G protein subunits, gap junction proteins, dominant negative mutants of such, truncated proteins, and insertion, deletion, and substitution mutant forms. See id. ¶¶ 0071-0082.

This disclosure of Marban, either alone or in combination with the other asserted references (see below), does not render obvious the use of HCN2. *Cf. Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359-60 (Fed. Cir. 2007) (affirming finding of nonobviousness in part because the prior art provided nothing to narrow the class of disclosed possible starting compounds). Applicants maintain that, by emphasizing a dominant negative form of HCN1, which would down-regulate HCN2 activity, Marban teaches away from the present compositions and methods, which use functional HCN2, not non-functional or inhibitory HCN2. Moreover, in view of the laundry list of various types of proteins useful in the invention, and the emphasis on dominant negative protein forms, the person of ordinary skill in the art would not have a reasonable expectation of success in using functional HCN2. Applicants therefore conclude that Marban, either alone or in combination with the other references, cannot form the basis for a finding of *prima facie* obviousness. In sum, it is unclear from where the necessary motivation or "reason" derives to combine and modify the reverse gene therapy taught by Levy and Marban to arrive at the gene therapy methods and compositions of the claims.

Marban further differs from the claimed methods by not teaching the use of hMSCs as a vehicle for the nucleic acids, as the Examiner appears to acknowledge. *See* Office Action at 9.

### C. Jansen

According to the Examiner, Jansen to teaches "a process comprising providing mammalian cells that express a hyperpolarization activated cation channel including HCN2 and determining the membrane potential of the cells." The Examiner acknowledges that Jansen does "not explicitly teach a composition of MSC comprising HCN2."

Jansen teaches a fluorescent screening assay that can be used to identify substances that modulate the activity of hyperpolarization-activated cation channels. *See* Jansen at col. 2, ll. 7-31. The mouse HCN2 gene was used to transform HEK and CHO cells. Since the most strongly-expressing CHO cells had only a weak current, HEK cells were used in the trial runs for the assay. *See id.* at col. 10, l. 40-col. 12, l. 8. Jansen does not disclose the use of MSCs. Jansen also teaches the use of wild-type HCN2.

**D. Wang**

According to the Examiner, Wang teaches "administration of MSC in the heart shows growth potential in a myocardial environment and indicated the formation of gap junctions suggesting that cells derived from marrow stromal cells, as well as native cardiomyocytes, are connected by intercalated disks." The Examiner acknowledges that Wang does "not teach composition comprising MSC [comprising] HCN2."

Wang teaches the administration of MSCs to a heart to mitigate or reverse the loss of heart cells that results from heart failure (via, e.g., necrosis or apoptosis). *See* Wang at 999, 1003-04. The disclosed method differs from the method claimed in the present application in several significant ways, including that the cells used in Wang are not incorporated with any DNA (let alone DNA that encodes HCN2), the cells used in Wang differentiate (in fact, differentiation is the desired outcome), and the condition treated in Wang is cardiac cell loss, not cardiac arrhythmia.

**E. References in Combination**

Despite these substantial differences between the teachings of the references and the claimed methods, the Examiner has pieced together selected portions of the references to assert that the claimed methods and compositions of the rejected claims are *prima facie* obvious over the references. Applicants contend that such a conclusion can be reached only by impermissible hindsight. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning," even though "a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ."). The

only references that have anything to do with gene therapy, Levy and Marban, teach away from the use of nucleic acids that encode proteins with wild-type or increased wild-type activity. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359 (Fed. Cir. 2007) (finding claims at issue not obvious in part because the prior art taught away from the claimed subject matter).

Applicants contend that the person of ordinary skill in the art would not combine Jansen's teaching with Marban or Levy, which teach methods that use dominant negative or non-wild-type proteins. Applicants thus conclude that the teachings of the references would not motivate the person of ordinary skill in the art to combine the references and to modify their teachings to arrive at the claimed compositions. The deficiencies of the references cannot be excused merely by stating that they are use in an obviousness rejection, not in an anticipation rejection.

As noted above, Wang relates to the implantation of MSCs into a heart that has suffered cell loss and Jansen relates to the use of HCN2 in vitro in screening assays. Neither of these provides the motivation to modify the prior art disclosure of Marban or Levy to arrive at the claimed compositions and methods and/or the reasonable expectation of success necessary to a finding of *prima facie* obviousness. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007) (affirming a finding of nonobviousness in part because the prior art provided no guidance in modifying the prior art to arrive at the claimed chemical compounds). There should be some articulated reason to modify the prior art, whether found in the references or otherwise. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotations omitted)). The Office Action fails to provide such a reason other than by impermissible hindsight.

Further, even if the person of ordinary skill in the art somehow were motivated to modify a teaching of reverse gene therapy to arrive at a method of gene therapy, there is no basis for finding a reasonable expectation of success. The cited references provide no actual disclosure of

experiments that were performed that successfully employed the disclosed reverse gene therapy methods. Also, this field is highly unpredictable, as the Examiner has pointed out. In the absence of any working example of the treatment of a model animal (as in the instant application) or actual subject, the person of ordinary skill in the art would not have had a reasonable expectation of success in employing the claimed gene therapy methods. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) (stating that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.")

In the absence of such a reasonable expectation of success, the person of ordinary skill in the art would not have been motivated to prepare the claimed compositions.

Applicants further note that the Examiner appears to base his argument on critical but unsupported assertions: that "it was generally known to one of ordinary skill in the art that HCN2 could be used to affect cardiac firing rate" (Office Action at 9-10, emphasis added) and "the art had already shown that HCN2 and other ion channel isoform[s] could be expressed in different cardiac or stem cell for pacemaker activity" (Office Action at 10, emphasis added). The cited prior art does not support these statements. In the absence of support, the Examiner's reliance on these statements is impermissible.

Applicants respectfully conclude that these obviousness rejections should be withdrawn as not supported by the cited prior art.

**F. Qu**

The Examiner raised the Qu reference (Jihong Qu et al., *HCN2 Overexpression in Newborn and Adult Ventricular Myocytes*, Circulation Research 89: e8-e14 (2001)) during the interview of April 15, 2008 (summarized above). Although the Examiner has not made a formal rejection of the pending claims based on Qu, Applicants will set forth why they believe Qu fails to render obvious the pending claims, either alone or in combination with the references cited in the Office Action.

First, Qu discloses an *in vitro* analysis of HCN2 incorporated into myocytes derived from

adult and neonatal rats. HCN2 activity was assessed using a whole-cell patch clamp method. *See* Qu at e8-e9. The authors found that HCN2 function varied according to whether it was incorporated into adult- or neonatal-derived cells. *See id.* at e9-e10. The authors conclude by stating that, "[a]s we gain further insight into the mechanisms regulating the voltage dependence of this gene family, it may be possible to control both the level of current and its activation voltage and thereby its contribution to an automatic rhythm." Qu at e13 (last sentence).

Applicants point out that, while Qu discloses results of HCN2 expression in heart-derived myocytes, the reference provides no teaching regarding expression of HCN2 in MSCs, a substantially different cell type, and no *in vivo* administration of cells incorporated with HCN2 with generation of pacemaker current. The other references do not compensate for these deficiencies.

Thus, Qu, alone or in combination with the other cited references, does not render the claims *prima facie* obvious at least because it fails to provide the reasonable expectation of success that the other references fail to provide, as set forth above. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) (stating that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.")

## V. Rejection of claims 20 and 65 under 35 U.S.C. §103(a) (Obviousness)

The Examiner rejected composition claims 20 and 65 under 35 U.S.C. §103(a) as allegedly unpatentable over Marban, Jansen, Wang, and Ruhparwar et al., *Transplanted fetal cardiomyocytes as cardiac pacemaker*, Eur. J. Cardiothorac. Surg. 21: 853-857 (2002) ("Ruhparwar"). According to the Examiner, Ruhparwar teaches a method comprising administering $2x10^6$ cardiomyocytes directly into the free wall of the left ventricle of X-linked muscular dystrophy-afflicted dogs that fail to express dystrophin in cardiac muscle, and demonstrates electrical and mechanical coupling between allogeneic donor cardiomyocytes and recipient myocardium *in vivo*. The Examiner stated that Ruhparwar emphasizes that cardiomyocytes engraftment could initiate further research aimed at generation of autologous cardiomyocytes preferably from pluripotent embryonic or adult stem cells or by achieving controlled proliferation of adult cardiomyocytes.

The Examiner also acknowledged that Ruhparwar does not teach a composition comprising MSC comprising HCN2 or a method of using such composition. Nevertheless, the Examiner asserted that it would have been obvious for one of ordinary skill in the art at the time of invention to modify the MSCs that express a nucleic acid encoding specific HCN isoforms as taught by Marban for expressing ion channel genes in a stem cell at a sufficient level for pacemaker activity.

Applicants respectfully disagree for the reasons set forth above with respect to Marban, Jansen and Wang and because the Ruhparwar reference does not remedy the deficiencies of the other references. In fact, it is not clear what Ruhparwar adds to the other three references. According to the Examiner, Ruhparwar shows "electrical and mechanical coupling between allogeneic donor cardiomyocytes and recipient myocardium *in vivo*." Office Action at 11. The Examiner also cites Ruhparwar for suggesting that the results obtained "could initiate further research" using adult stem cells. *See id.* at 11 (citing Ruhparwar at 857).

Applicants note again that the cells in Ruhparwar are not genetically modified, unlike those in the Applicants' compositions. Further, that Ruhparwar's "study could initiate further research" (Ruhparwar at 857) is merely speculation about the utility of adult stem cells that would need to be born out by "further research." Such further research would be with non-genetically-modified cells. Thus, in view of our comments above, at best the cited references would motivate the person of ordinary skill in the art to prepare a composition that could be used in reverse gene therapy or a composition that contains non-genetically-modified cells. There would be no reasonable expectation of success with respect to the utility of other compositions, such as the claimed compositions, and therefore no motivation to prepare them. It is only by impermissible hindsight that a motivation to prepare the claimed compositions with a reasonable expectation of success can be derived from the cited references. There must be some articulated reason to modify the prior art, whether found in the references or otherwise. The Office Action fails to provide such a reason other than by impermissible hindsight.

In sum, as noted above, alone or in combination, Marban, Jansen, or Wang do not

disclose or suggest a composition comprising MSCs incorporated with a nucleic acid encoding HCN2, wherein the MSC forms a gap junction with a cell of a mammalian heart in the absence of differentiation of the MSC. Applicants assert that, in teaching the administration of differentiated cardiomyocytes into the heart, Ruhparwar does not remedy the deficiencies of Marban, Jansen, and Wang in this regard. Thus, for at least this reason, Applicants maintain that claims 20 and 65 are not rendered obvious by the combination of Marban, Jansen, Wang, and Ruhparwar. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

## VI. Double Patenting Rejections

The Examiner maintained the provisional rejection of claims 20, 49, 51, 56-57 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 20-59 of co-pending Application No. 10/342,506 ("the '506 application), which corresponds to U.S. Publication No. 20040137621.

Applicants again note that this is a "provisional" rejection over the '506 application which is not an allowed application. Accordingly, if the now pending claims of the subject application are otherwise allowable, the present provisional double patenting rejections should be withdrawn and the claims in the subject application should be allowed and issued, whereby the claims of the '506 application would become subject to an obviousness-type double patenting rejection. At that time, applicant will consider filing a terminal disclaimer, if necessary.

## CONCLUSION

In view of the remarks made hereinabove, Applicants respectfully request that the Examiner reconsider and withdraw the rejections set forth in the November 2, 2007 Final Office Action, and earnestly solicits allowance of the now pending claims.

If a telephone interview would assist in expediting prosecution of the subject application, the Examiner is invited to telephone the undersigned at the number provided below. No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is

required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 11-0600.

Respectfully submitted,

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